

**This Page Is Inserted by IFW Operations  
and is not a part of the Official Record**

## **BEST AVAILABLE IMAGES**

**Defective images within this document are accurate representation of  
The original documents submitted by the applicant.**

**Defects in the images may include (but are not limited to):**

- **BLACK BORDERS**
- **TEXT CUT OFF AT TOP, BOTTOM OR SIDES**
- **FADED TEXT**
- **ILLEGIBLE TEXT**
- **SKEWED/SLANTED IMAGES**
- **COLORED PHOTOS**
- **BLACK OR VERY BLACK AND WHITE DARK PHOTOS**
- **GRAY SCALE DOCUMENTS**

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning documents *will not* correct images,  
please do not report the images to the  
Image Problem Mailbox.**

**THIS PAGE BLANK (USPTO)**

## PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : A61K 31/445, 31/40		A1	(11) International Publication Number: WO 97/16190
			(43) International Publication Date: 9 May 1997 (09.05.97)
(21) International Application Number: PCT/US96/13624		(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 26 August 1996 (26.08.96)			
(30) Priority Data: 08/551,026 31 October 1995 (31.10.95) US 08/645,149 13 May 1996 (13.05.96) US			
(71) Applicant: GUILFORD PHARMACEUTICALS INC. [US:US]; 6511 Tributary Street, Baltimore, MD 21224 (US).		Published With international search report.	
(72) Inventors: STEINER, Joseph, P.; 988 Sugar Maple Street, Hampstead, MD 21074 (US). HAMILTON, Gregory, S.; 6501 Frederick Road, Catonsville, MD 21228 (US).			
(74) Agent: NATH, Gary, M.; Nath & Associates, Suite 750, 1835 K Street, N.W., Washington, DC 20006-1203 (US).			
(54) Title: ROTAMASE ENZYME ACTIVITY INHIBITORS			
(57) Abstract			
<p>This invention relates to the method of using specially formulated neurotrophic pipecolic acid derivative compounds having an affinity for FKBP-type immunophilins as inhibitors of the enzyme activity associated with immunophilin proteins, and particularly inhibitors of peptidyl-prolyl isomerase or rotamase enzyme activity to stimulate or promote neuronal growth or regeneration.</p>			

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

ROTAMASE ENZYME ACTIVITY INHIBITORSRelated Application

5 This application is a continuation-in-part application of U.S. Patent Application Serial No. 08/551,026 filed October 31, 1995.

BACKGROUND OF THE INVENTION

10

1. Field of the Invention

This invention relates to the method of using neurotrophic FKBP inhibitor compounds having an affinity for FKBP-type immunophilins as inhibitors of the enzyme activity associated with immunophilin proteins, and particularly inhibitors of peptidyl-prolyl isomerase or rotamase enzyme activity.

2. Description of the Prior Art

20

The term immunophilin refers to a number of proteins that serve as receptors for the principal immunosuppressant drugs, cyclosporin A (CsA), FK506, and rapamycin. Known classes of immunophilins are cyclophilins, and FK506 binding proteins, such as FKBP. Cyclosporin A binds to cyclophilin while FK506 and rapamycin bind to FKBP. These immunophilin-drug complexes interface with a variety of intracellular signal transduction systems, especially in the immune system and the nervous system.

30

Immunophilins are known to have peptidyl-prolyl isomerase (PPIase) or rotamase enzyme activity. It has been determined that rotamase activity has a role in the catalyzation of the interconversion of

**SUBSTITUTE SHEET (RULE 26)**

the cis and trans isomer of immunophilin proteins.

Immunophilins were originally discovered and studied in immune tissue. It was initially postulated by those skilled in the art that inhibition of the immunophilins rotamase activity leads to the inhibition of T-cell proliferation, thereby causing the immunosuppressive action exhibited by immunosuppressive drugs such as cyclosporin A, FK506, and rapamycin. Further study has shown that the inhibition of rotamase activity, in and of itself, is not sufficient for immunosuppressant activity. Instead immunosuppression appears to stem from the formulation of a complex of immunosuppressant drugs and immunophilins. It has been shown that the immunophilin-drug complexes interact with ternary protein targets as their mode of action. In the case of FKBP-FK506 and FKBP-CsA, the drug-immunophilin complexes bind to the enzyme calcineurin, inhibiting T-cell receptor signalling leading to T-cell proliferation. Similarly, the complex of rapamycin and FKBP interacts with the RAFT1/FRAP protein and inhibits signalling from the IL-2 receptor.

Immunophilins have been found to be present at high concentrations in the central nervous system. Immunophilins are enriched 10-50 times more in the central nervous system than in the immune system.

Within neural tissues, immunophilins appear to influence nitric oxide synthesis, neurotransmitter release, and neuronal process extension.

FK506 also augments the phosphorylation of growth-associated protein-43 (GAP43). GAP43 is involved in neuronal process extension and its phosphorylation appears to augment this activity. Accordingly, the effects of FK506 rapamycin and cyclosporin in neuronal process extension have been examined using PC12 cells. PC12 cells are a continuous line of neuronal-like cells which extend neurites when stimulated by nerve growth factor (NGF).

Surprisingly, it has been found that picomolar concentrations of an immunosuppressant such as FK506 and rapamycin stimulate neurite out growth in PC12 cells and sensory neurons, namely dorsal root ganglion cells (DRGs). In whole animal experiments, FK506 has been shown to stimulate nerve regeneration following facial nerve injury and results in functional recovery in animals with sciatic nerve lesions.

More particularly, it has been found that drugs with a high affinity for FKBP are potent rotamase inhibitors and exhibit excellent neurotrophic effects. Snyder et al., "Immunophilins and the Nervous System", Nature Medicine, Volume 1, No. 1, January 1995, 32-37. These findings suggest the use

of immunosuppressants in treating various peripheral neuropathies and enhancing neuronal regrowth in the central nervous system (CNS). Studies have demonstrated that neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease may occur due to the loss, or decreased availability, of a neurotrophic substance specific for a particular population of neurons affected in the disorder.

Several neurotrophic factors effecting specific neuronal populations in the central nervous system have been identified. For example, it has been hypothesized that Alzheimer's disease results from a decrease or loss of nerve growth factor (NGF). It has thus been proposed to treat SDAT patients with exogenous nerve growth factor or other neurotrophic proteins such as brain derived growth factor, glial derived growth factor, ciliary neurotrophic factor, and neurotrophin-3 to increase the survival of degenerating neuronal populations.

Clinical application of these proteins in various neurological disease states is hampered by difficulties in the delivery and bioavailability of large proteins to nervous system targets. By contrast, immunosuppressant drugs with neurotrophic activity are relatively small and display excellent bioavailability and specificity. However, when administered chronically, immunosuppressants exhibit a number of potentially serious side effects



including nephrotoxicity, such as impairment of glomerular filtration and irreversible interstitial fibrosis (Kopp et al., 1991, *J. Am. Soc. Nephrol.* 1:162); neurological deficits, such as involuntary tremors, or non-specific cerebral angina such as non-localized headaches (De Groen et al., 1987, *N. Engl. J. Med.* 317:861); and vascular hypertension with complications resulting therefrom (Kahan et al., 1989 *N. Engl. J. Med.* 321: 1725).

The present invention provides non-immunosuppressive FKBP inhibitor compounds containing small molecule FKBP rotamase inhibitors which are extremely potent in augmenting neurite outgrowth, and for promoting neuronal growth, and regeneration in various neuropathological situations where neuronal repair can be facilitated including peripheral nerve damage by physical injury or disease state such as diabetes, physical damage to the central nervous system (spinal cord and brain), brain damage associated with stroke, and for the treatment of neurological disorders relating to neurodegeneration, including Parkinson's disease and Alzheimer's disease.

#### SUMMARY OF THE INVENTION

This invention relates to the method of using neurotrophic FKBP inhibitor compounds having an affinity for FKBP-type immunophilins as inhibitors of the enzyme activity associated with immunophilin

proteins, and particularly inhibitors of peptidyl-prolyl isomerase or rotamase enzyme activity.

A preferred embodiment of this invention is a method of treating a neurological activity in an animal, comprising: administering to an animal an effective amount of a FKBP inhibitor having an affinity for FKBP-type immunophilins to stimulate growth of damaged peripheral nerves or to promote neuronal regeneration, wherein the FKBP-type immunophilin exhibits rotamase activity and the  
10      pipecolic acid derivative inhibits said rotamase activity of the immunophilin.

Another preferred embodiment of this invention is a method of treating a neurological disorder in an animal, comprising: administering to an animal  
15      an effective amount of a FKBP inhibitor having an affinity for FKBP-type immunophilins in combination with an effective amount of a neurotrophic factor selected from the group consisting of neurotrophic growth factor, brain derived growth factor, glial  
20      derived growth factor, ciliary neurotrophic factor, and neurotrophin-3, to stimulate growth of damaged peripheral nerves or to promote neuronal regeneration, wherein the FKBP-type immunophilin  
25      exhibits rotamase activity and the pipecolic acid derivative inhibits said rotamase activity of the immunophilin.

Another preferred embodiment of this invention

is a method of stimulating growth of damaged peripheral nerves, comprising: administering to damaged peripheral nerves an effective amount of an FKBP inhibitor compound having an affinity for FKBP-type immunophilins to stimulate or promote growth of the damaged peripheral nerves, wherein the FKBP-type immunophilins exhibit rotamase activity and the pipecolic acid derivative inhibits said rotamase activity of the immunophilin.

10 Another preferred embodiment of this invention is a method of stimulating growth of damaged peripheral nerves, comprising: administering to damaged peripheral nerves an effective amount of an FKBP inhibitor compound having an affinity for FKBP-type immunophilins to stimulate growth of damaged peripheral nerves, wherein the FKBP-type immunophilin exhibit rotamase activity and the pipecolic acid derivative inhibits said rotamase activity of the immunophilin.

20 Another preferred embodiment of this invention is a method for promoting neuronal regeneration and growth in animals, comprising: administering to an animal an effective amount of an FKBP inhibitor compound having an affinity for FKBP-type immunophilins to promote neuronal regeneration, wherein the FKBP-type immunophilins exhibit rotamase activity and the pipecolic acid derivative inhibits said rotamase activity of the immunophilin.

Yet another preferred embodiment of this invention is a method for preventing neurodegeneration in an animal, comprising: administering to an animal an effective amount of an FKBP inhibitor having an affinity for FKBP-type immunophilins to prevent neurodegeneration, wherein the FKBP-type immunophilin exhibits rotamase activity and the pipecolic acid derivative inhibits said rotamase activity of the immunophilin.

10

#### BRIEF DESCRIPTION OF THE DRAWINGS

15

FIG. 1 is a dose-response curve for Example 15. Fig. 1 shows the data from 6-10 different concentrations used to generate typical dose-response curves, from which  $ED_{50}$  values were calculated.

20

FIG. 2 is a dose-response curve for Example 22. Fig. 2 shows the data from 6-10 different concentrations used to generate typical dose-response curves, from which  $ED_{50}$  values were calculated.

25

FIG. 3 is a representative photomicrograph of a sensory neuron responding to trophic effects of the drugs. Fig. 3 shows the dose-response for Example 21 in cultured sensory neurons.

FIG. 4 is a representative photomicrograph of a sensory neuron responding to trophic effects of the drugs. Fig. 4 shows the effect of 300 pM of Example 15 on neurite outgrowth in cultured sensory neurons.

FIG. 5 is a representative photomicrograph of a sensory neuron responding to trophic effects of the drugs. Fig. 5 shows the effect of 1 nM of Example 22 on neurite outgrowth in cultured sensory neurons.

5

#### DETAILED DESCRIPTION OF THE INVENTION

The novel neurotrophic FKBP inhibitor compounds of this invention have an affinity for the FK506 binding proteins such as FKBP-12. When the neurotrophic compounds of the invention are bound to  
10 FKBP, they have been found to inhibit the prolyl-peptidyl cis-trans isomerase activity, or rotamase activity of the binding protein and unexpectedly stimulate neurite growth.

The compounds of the present invention can be  
15 used in the form of salts derived from inorganic or organic acids and bases. Included among such acid salts are the following: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate butyrate, citrate, camphorate,  
20 camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemissulfate heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate,  
25 lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, propionate, succinate, tartrate, thiocyanate, tosylate and undecanoate. Base salts

include ammonium salts, alkali metal salts such as sodium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salt with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth. Also, the basic nitrogen-containing groups can be quarternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates such as dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; aralkyl halides like benzyl and phenethyl bromides; and others.

Water or oil-soluble or dispersible products are thereby obtained.

The neurotrophic compounds of this invention can be periodically administered to a patient undergoing treatment for neurological disorders or for other reasons in which it is desirable to stimulate neuronal regeneration and growth, such as in various peripheral neuropathic and neurological disorders relating to neurodegeneration. The compounds of this invention can also be administered to mammals other than humans for treatment of various mammalian neurological disorders.

The novel compounds of the present invention are potent inhibitors of rotamase activity and

possess an excellent degree of neurotrophic activity. This activity is useful in the stimulation of damaged neurons, the promotion of neuronal regeneration, the prevention of neurodegeneration, and in the treatment of several neurological disorders known to be associated with neuronal degeneration and peripheral neuropathies. The neurological disorders that may be treated include but are not limited to: trigeminal neuralgia, glossopharyngeal neuralgia, Bell's Palsy, myasthenia gravis, muscular dystrophy, progressive muscular atrophy, progressive bulbar inherited muscular atrophy, herniated, ruptured or prolapsed intervertebral disk syndromes, cervical spondylosis, plexus disorders, thoracic outlet destruction syndromes, peripheral neuropathic such as those caused by lead, dapsone, ticks, porphyria, or Guillain-Barré syndrome, Alzheimer's disease, and Parkinson's disease.

For these purposes the compounds of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir in dosage formulations containing conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous, intravenous, intramuscular, intraperitoneally, intrathecally,

intraventricularly, intrasternal and intracranial injection or infusion techniques.

To be effective therapeutically as central nervous system targets, the immunophilin-drug complex should readily penetrate the blood-brain barrier when peripherally administered. Compounds of this invention which cannot penetrate the blood-brain barrier can be effectively administered by an intraventricular route.

The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids such as oleic acid and its glyceride derivatives find use in the



preparation of injectables, olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant.

5           The compounds may be administered orally in the form of capsules or tablets, for example, or as an aqueous suspension or solution. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating  
10           agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is  
15           combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

          The compounds of this invention may also be administered in the form of suppositories for rectal  
20           administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the  
25           drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

          The compounds of this invention may also be administered optically, especially when the

conditions addressed for treatment involve areas or organs readily accessible by topical application, including neurological disorders of the eye, the skin, or the lower intestinal tract. Suitable  
5      topical formulations are readily prepared for each of these areas.

For ophthalmic use, the compounds can be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as  
10      solutions is isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively for the ophthalmic uses the compounds may be formulated in an ointment such as petrolatum.

15      For application topically to the skin, the compounds can be formulated in a suitable ointment containing the compound suspended or dissolved in, for example, a mixture with one or more of the following: mineral oil, liquid petrolatum, white  
20      petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the compounds can be formulated in a suitable lotion or cream containing the active compound suspended or dissolved in, for  
25      example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation.

5 Dosage levels on the order of about 0.1 mg to about 10,000 mg of the active ingredient compound are useful in the treatment of the above conditions, with preferred levels of about 0.1 mg to about 1,000 mg. The amount of active ingredient that may be  
10 combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

It is understood, however, that a specific dose level for any particular patient will depend upon a  
15 variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the severity of the particular disease being treated and  
20 form of administration.

The compounds can be administered with other neurotrophic agents such as neurotrophic growth factor (NGF), glial derived growth factor, brain  
derived growth factor, ciliary neurotrophic factor,  
25 and neurotrophin-3. The dosage level of other neurotrophic drugs will depend upon the factors previously stated and the neurotrophic effectiveness of the drug combination.

Methods and Procedures

Nerve Extension Elicited in Chick Dorsal Root  
Ganglia by Non-Immunosuppressive Ligands of  
Immunophilins

5           In previous studies, it has been observed that  
neurotrophic effects of immunosuppressant drugs in  
explants of rat dorsal root ganglia with significant  
augmentation in nerve outgrowth has occurred with  
FK506 concentrations as low as 1 picomolar (Lyons  
10 et. al., 1994). In the rat ganglia neurotrophic  
effects were observed with FK506 even in the absence  
of NGF. In the present work explants of chick  
dorsal root ganglia have been used, which are easier  
to employ in studies of nerve outgrowth. In the  
15 absence of added NGF, we have observed minimal  
effects of immunophilin ligand drugs. The chick  
cells are more sensitive to NGF than PC-12 cells so  
that we employ 0.1 ng/ml NGF to produce minimal  
neurite outgrowth and to demonstrate neurotrophic  
20 actions of immunophilin ligands (Fig. 5).

          The maximal increase in the number of  
processes, their length and branching is quite  
similar at maximally effective concentrations of the  
immunophilin ligands and of NGF (100 ng/ml). With  
25 progressively increasing concentrations of the  
various drugs, one observes a larger number of  
processes, more extensive branching and a greater  
length of individual processes.

We evaluated the potencies of drugs in binding to FKBP-12 by examining inhibition of peptidyl prolyl-isomerase activity and inhibition of <sup>3</sup>H-FK506 binding to recombinant FKBP-12 (Table 1). There is  
5 a striking parallel between their potencies in stimulating neurite outgrowth and inhibiting rotamase activity.

The very close correlation between the potencies of drugs in binding to immunophilins,  
10 inhibiting their rotamase activity and stimulating neurite outgrowth implies that inhibition of rotamase activity is responsible for neurotrophic effects of the drugs. The extraordinarily high  
15 potency of the drugs in stimulating neurite outgrowth and in binding to immunophilins makes it most unlikely that any other target could account for the neurotrophic effects.

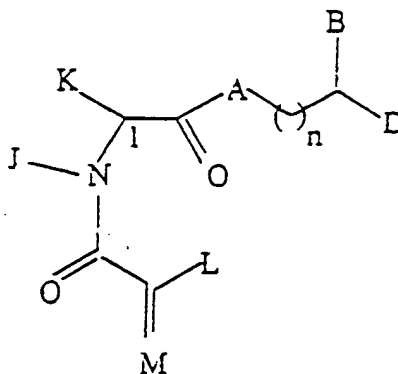
Because of the extraordinary potency of the drugs and the close correlation between rotamase  
20 inhibition and neurotrophic actions, we conclude that rotamase inhibition is likely involved in neurotrophic effects. A number of proteins have been reported as substrates for the rotamase  
25 activity of immunophilins including collagen (Steinmann et. al., 1991) and transferring (Lodish and King, 1991). Recently highly purified preparations of ryanodine receptor and the IP-3 receptor, prominent intracellular calcium channels,

have been reported to exist in a complex with FKBP-12. Dissociation of FKBP-12 from these complexes causes the calcium channels to become "leaky" (Cameron et. al., 1995). Calcium fluxes are  
5 involved in neurite extension so that the IP-3 receptor and the ryanodine receptor might be involved in the neurotrophic effects of drugs. Since the drugs bind to the same site on FKBP-12 as the IP-3 receptor or the ryanodine receptor, one  
10 would have to postulate that the drugs displace the channels from FKBP-12. No interaction between these calcium channels in cyclophilin has been reported so that this model would not explain the neurotrophic actions of cyclosporin A.

15 The neurotrophic actions of the drugs studied here are exerted at extremely low concentrations indicating potencies comparable to those of neurotrophic proteins such as brain derived growth factor, neurotrophin-3 and neurotrophic growth  
20 factor.

The following examples are illustrative of preferred embodiments of the invention and are not to be construed as limiting the invention thereto. All polymer molecular weights are mean average  
25 molecular weights. All percentages are based on the percent by weight of the final delivery system or formulation prepared unless otherwise indicated and all totals equal 100% by weight.

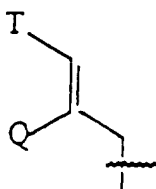
Illustrative generic FKBP inhibitor compounds  
which can be used for the purposes of this invention  
include:



and pharmaceutically acceptable salts thereof,

wherein A is CH<sub>2</sub>, O, NH, or N-(C<sub>1</sub>-C<sub>4</sub> alkyl);

wherein B and D are independently Ar, (C<sub>5</sub>-C<sub>7</sub>)-  
cycloalkyl substituted (C<sub>1</sub>-C<sub>6</sub>)-straight or branched  
alkyl or alkenyl, (C<sub>5</sub>-C<sub>7</sub>)-cycloalkenyl substituted  
(C<sub>1</sub>-C<sub>6</sub>)-straight or branched alkyl or alkenyl, or Ar  
substituted (C<sub>1</sub>-C<sub>6</sub>)-straight or branched alkyl or  
alkenyl, wherein in each case, one or two carbon  
atoms of the straight or branched alkyl or alkenyl  
groups may be substituted with 1-2 heteroatoms  
selected from the group consisting of oxygen,  
sulfur, SO and SO<sub>2</sub> in chemically reasonable  
substitution patterns, or



wherein Q is hydrogen, (C1-C6)-straight or  
5 branched alkyl or (C1-C6)-straight or branched  
alkenyl;

wherein T is Ar or substituted 5-7 membered  
cycloalkyl with substituents at positions 3 and 4  
which are independently selected from the group  
10 consisting of hydrogen, hydroxyl, O-(C1-C4)-alkyl or  
O-(C1-C4)-alkenyl and carbonyl;

wherein Ar is selected from the group  
consisting of 1-naphthyl, 2-naphthyl, 2-furyl, 3-  
furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl,  
15 4-pyridyl and phenyl, monocyclic and bicyclic  
heterocyclic ring systems with individual ring sizes  
being 5 or 6 which may contain in either or both  
rings a total of 1-4 heteroatoms independently  
selected from oxygen, nitrogen and sulfur; wherein  
20 Ar may contain one to three substituents which are  
independently selected from the group consisting of  
hydrogen, halo, hydroxyl, hydroxymethyl, nitro, CF<sub>3</sub>,  
trifluoromethoxy, (C1-C6)-straight or branched alkyl  
or (C1-C6)-straight or branched alkenyl, O-(C1-C4)-  
25 straight or branched alkyl or O-(C1-C4)-straight or  
branched alkenyl, O-benzyl, O-phenyl, amino, 1,2-  
methylenedioxy, carbonyl and phenyl;

wherein L is either hydrogen or U; M is either



oxygen or CH-U, provided that if L is hydrogen, then M is CH-U, or if M is oxygen then L is U;

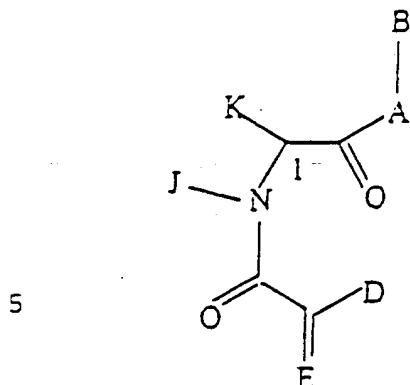
wherein U is hydrogen, O-(C1-C4)-straight or branched alkyl or O-(C1-C4)-straight or branched alkenyl, (C1-C6)-straight or branched alkyl or (C1-C6)-straight or branched alkenyl, (C5-C7)-cycloalkyl, (C5-C7)-cycloalkenyl substituted with (C1-C4)-straight or branched alkyl or (C1-C4)-straight or branched alkenyl, [(C1-C4)-alkyl or (C1-C4)-alkenyl]-Ar or Ar (Ar as described above);

wherein J is hydrogen or C1 or C2 alkyl or benzyl; K is (C1-C4)-straight or branched alkyl, benzyl or cyclohexylethyl; or wherein J and K may be taken together to form a 5-7 membered heterocyclic ring which may contain an oxygen (O), sulfur (S), SO or SO<sub>2</sub> substituted therein; and

wherein n is 0-3.

The stereochemistry at position 1 (Formula I) is (R) or (S), with (S) preferred. The stereochemistry at position 2 is (R) or (S).

Illustrative preferred FKBP inhibitor compounds which can be used for the purposes of this invention are described in U.S. Patent No. 5,330,993, the contents of which is incorporated herein by reference. Exemplary compounds include those having the formula:



and pharmaceutically acceptable salts thereof,

wherein A is O, NH, or N-(C1-C4 alkyl);

wherein B is hydrogen, CHL-Ar, (C1-C6)-straight  
 10 or branched alkyl, (C1-C6)-straight or branched  
 alkenyl, (C5-C7)-cycloalkyl, (C5-C7)-cycloalkenyl or  
 Ar substituted (C1-C6)-alkyl or alkenyl, or



wherein L and Q are independently hydrogen,  
 (C1-C6)-straight or branched alkyl or (C1-C6)-  
 straight or branched alkenyl;

20 wherein T is Ar or substituted cyclohexyl with  
 substituents at positions 3 and 4 which are  
 independently selected from the group consisting of  
 hydrogen, hydroxyl, O-(C1-C4)-alkyl or O-(C1-C4)-  
 alkenyl and carbonyl;

25 wherein Ar is selected from the group  
 consisting of 1-naphthyl, 2-naphthyl, 2-furyl, 3-  
 furyl, 2-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl  
 and phenyl having one to three substituents which

are independently selected from the group consisting of hydrogen, halo, hydroxyl, nitro, CF<sub>3</sub>, (C1-C6)-straight or branched alkyl or (C1-C6)-straight or branched alkenyl, O-(C1-C4)-straight or branched alkyl or O-(C1-C4)-straight or branched alkenyl, O-benzyl, O-phenyl, amino and phenyl;

wherein D is either hydrogen or U; E is either oxygen or CH-U, provided that if D is hydrogen, then E is CH-U, or if E is oxygen then D is U;

wherein U is hydrogen, O-(C1-C4)-straight or branched alkyl or O-(C1-C4)-straight or branched alkenyl, (C1-C6)-straight or branched alkyl or (C1-C6)-straight or branched alkenyl, (C5-C7)-cycloalkyl, (C5-C7)-cycloalkenyl substituted with (C1-C4)-straight or branched alkyl or (C1-C4)-straight or branched alkenyl, 2-indolyl, 3-indolyl, [(C1-C4)-alkyl or (C1-C4)-alkenyl]-Ar or Ar (Ar as described above);

wherein J is hydrogen or C1 or C2 alkyl or benzyl; K is (C1-C4)-straight or branched alkyl, benzyl or cyclohexylethyl; or wherein J and K may be taken together to form a 5-7 membered heterocyclic ring which may contain an oxygen (O), sulfur (S), SO or SO<sub>2</sub> substituted therein.

The stereochemistry at position 1 (Formula I) is (R) or (S), with (S) preferred.

#### K<sub>1</sub> Test Procedure

Inhibition of the peptidyl-prolyl isomerase

(rotamase) activity of the compounds used herein can be evaluated by known methods described in the literature (Harding, M.W. et al. *Nature* 341: 758-760 (1989); Holt et al. *J. Am. Chem. Soc.* 115: 9923-9938). These values are obtained as apparent  $k$ 's and are presented for various compounds in Table I. The *cis-trans* isomerization of an alanine-proline bond in a model substrate, N-succinyl-Ala-Ala-Pro-Phe-*p*-nitroanilide, is monitored spectrophotometrically in a chymotrypsin-coupled assay, well known to those skilled in the art, which releases *para*-nitroanilide from the *trans* form of the substrate. The inhibition of this reaction caused by the addition of different concentrations of inhibitor is determined, and the data is analyzed as a change in first-order rate constant as a function of inhibitor concentration to yield the apparent  $k$  values.

In a plastic cuvette are added 950  $\mu$ L of ice cold assay buffer (25 mM HEPES, pH 7.8, 100 mM NaCl), 10  $\mu$ L of FKBP (2.5 mM in 10 mM Tris-Cl pH 7.5, 100 mM NaCl, 1 mM dithiothreitol), 25  $\mu$ L of chymotrypsin (50 mg/mL in 1 mM HCl) and 10  $\mu$ L of test compound at various concentrations in dimethyl sulfoxide. The reaction is initiated by the addition of 5  $\mu$ L of substrate (succinyl-Ala-Phe-Pro-Phe-*para*-nitroanilide, 5 mg/mL in 2.35 mM LiCl in trifluoroethanol).

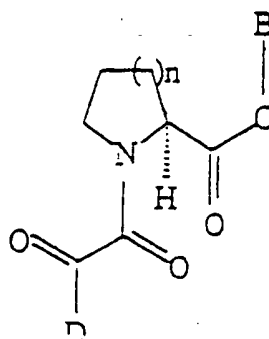
The absorbance at 390 nm versus time is

**SUBSTITUTE SHEET (RULE 26)**

monitored for 90 sec using a spectrophotometer and the rate constants are determined from the absorbance versus time data files.

The data for these experiments is presented in  
5 Tables I and IV.

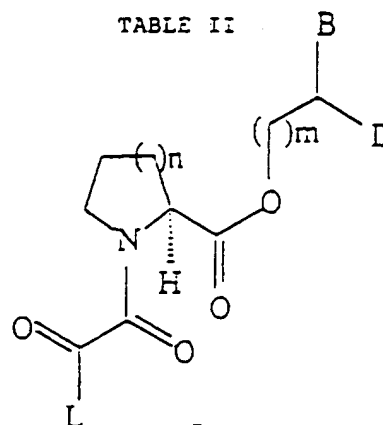
TABLE I



No.	B	D	n	K
1	Benzyl	Phenyl	2	1.5 $\mu\text{M}$
2	3-Phenylpropyl	Phenyl	2	
3	4-(4-Methoxy-phenyl)butyl	Phenyl	2	
4	4-Phenylbutyl	Phenyl	2	0.35 $\mu\text{M}$
5	Phenethyl	Phenyl	2	1.1 $\mu\text{M}$
6	4-Cyclohexyl-butyl	Phenyl	2	0.4 $\mu\text{M}$
7	Benzyl	Methoxy	2	80 $\mu\text{M}$
8	4-Cyclohexyl-butyl	Methoxy	2	6 $\mu\text{M}$
9	3-Cyclohexyl-propyl	Methoxy	2	20 $\mu\text{M}$
10	3-Cyclopentyl-propyl	Methoxy	2	35 $\mu\text{M}$
11	Benzyl	2-Furyl	2	3 $\mu\text{M}$
12	4-Cyclohexyl-butyl	3,4,5-Trimethoxy-phenyl	2	0.04 $\mu\text{M}$
13	3-Phenoxy-benzyl	3,4,5-Trimethoxy-phenyl	2	0.018 $\mu\text{M}$
14	4-Phenylbutyl	3,4,5-Trimethoxy-phenyl	2	0.019 $\mu\text{M}$
15	3-(3-Indolyl)propyl	3,4,5-Trimethoxy-phenyl	2	0.017 $\mu\text{M}$
16	4-(4-Methoxy-phenyl)butyl	3,4,5-Trimethoxy-phenyl	2	0.013 $\mu\text{M}$

27

TABLE II



No.	n	m	B	L	n	I
17	2	0	3-Phenylpropyl		3-(3-Pyridyl)propyl	Phenyl
18	2	0	3-Phenylpropyl		3-(2-Pyridyl)propyl	Phenyl
19	2	0	3-Phenylpropyl		2-(4-Methoxyphenyl)ethyl	Phenyl
20	2	0	3-Phenylpropyl		3-Phenylpropyl	Phenyl
21	2	0	3-Phenylpropyl		3-Phenylpropyl	3,4,5-Trimethoxyphenyl
22	2	0	3-Phenylpropyl		2-(3-Pyridyl)	3,4,5-Trimethoxyphenyl
23	2	0	3-Phenylpropyl		3-(2-Pyridyl)	3,4,5-Trimethoxyphenyl
24	2	0	3-Phenylpropyl		3-(4-Methoxyphenyl)propyl	3,4,5-Trimethoxyphenyl
25	2	0	3-Phenylpropyl		3-(3-Pyridyl)propyl	3-Iso-propoxyphenyl

Chick Dorsal Root Ganglion  
Cultures and Neurite Outgrowth

Dorsal root ganglia were dissected from chick embryos of ten day gestation. Whole ganglion explants were cultured on thin layer Matrigel-coated 12 well plates with Liebovitz L15 plus high glucose media supplemented with 2mM glutamine and 10% fetal calf serum, and also containing 10  $\mu$ M cytosine  $\beta$ -D arabinofuranoside (Ara C) at 37°C in an environment containing 5% CO<sub>2</sub>. Twenty-four hours later, the DRGs were treated with various concentrations of nerve

growth factor, immunophilin ligands or combinations of NFG plus drugs. Forty-eight hours after drug treatment, the ganglia were visualized under phase contrast or Hoffman Modulation contrast with a Zeiss Axiovert inverted microscope. Photomicrographs of the explants were made, and neurite outgrowth was quantitated. Neurites longer than the DRG diameter were counted as positive, with total number of neurites quantitated per each experimental condition. Three to four DRGs are cultured per well, and each treatment was performed in duplicate. Data from 6-10 different concentrations were used to generate dose-response curves, from which  $ED_{50}$  values were calculated. Typical response curves are shown in Figures 1 and 2 for examples 15 and 22, respectively.

Data for these experiments are presented in Tables III and IV. Representative photomicrographs of sensory neurons responding to the trophic effects of the drugs are shown in Figures 3-5. Fig. 3 demonstrates the dose-dependent neurotrophic effects of example 21 on neuronal cultures. Figure 4 demonstrates the stimulation of neurite outgrowth induced by a 300 pM dose of example 15 and, Fig. 5 demonstrates the stimulation of neurite outgrowth



induced by a 1nM dose of example 22.

Table III  
Neurite Outgrowth in Chick DRG

5	Example	ED <sub>50</sub> , nM Neurite Outgrowth in DRG cultures
	1	25-100
	2	10-20
	3	0.500
	4	25-100
10	5	25-100
	6	10-20
	7	>10,000
	8	>10,000
	9	>10,000
15	10	>10,000
	11	1000
	12	0.031
	13	0.180
	14	1-5
20	15	0.055
	16	0.030

Table IV

## Biological Results

5	Compound	K, nM	ED <sub>50</sub> , nM
.	in		Neurite Outgrowth DRG cultures
10	17	56	1-5
	18	50	0.063
	19	270	10-20
	20	---	0.0044
15	21	1.0	0.61
	22	3.0	0.95
	23	1.0	25
	24	3.0	0.50
20	25	2.0	0.30

25

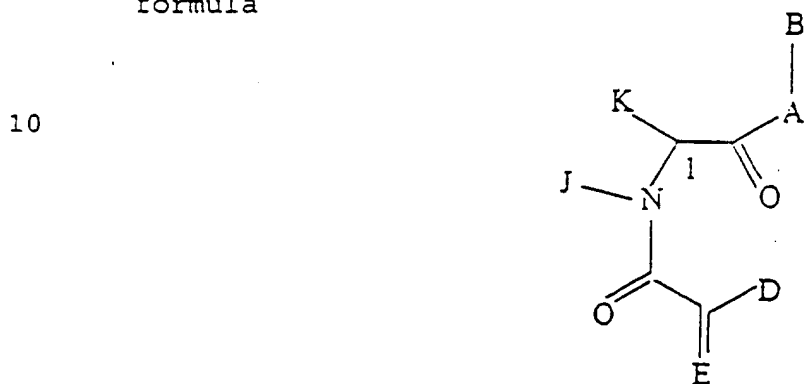
The invention being thus described, it will be obvious that the same may be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the invention and all such modifications are intended to be included within the scope of the following claims.

30

What is claimed is:

1. A method of treating a neurological activity in  
 5 an animal, comprising:

administering to an animal an effective amount  
 of a pipecolic acid derivative represented by the  
 formula



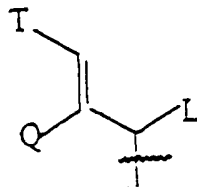
15

and pharmaceutically acceptable salts thereof,

wherein A is CH<sub>2</sub>, O, NH, or N-(C1-C4 alkyl);

wherein B and D are independently Ar, (C5-C7)-  
 cycloalkyl substituted (C1-C6)-straight or branched  
 20 alkyl or alkenyl, (C5-C7)-cycloalkenyl substituted  
 (C1-C6)-straight or branched alkyl or alkenyl, or Ar  
 substituted (C1-C6)-straight or branched alkyl or  
 alkenyl, wherein in each case, one or two carbon  
 atoms of the straight or branched alkyl or alkenyl  
 25 groups may be substituted with 1-2 heteroatoms  
 selected from the group consisting of oxygen,  
 sulfur, SO and SO<sub>2</sub> in chemically reasonable  
 substitution patterns, or

5



wherein Q is hydrogen, (C1-C6)-straight or  
 branched alkyl or (C1-C6)-straight or branched  
 10 alkenyl;

wherein T is Ar or substituted 5-7 membered  
 cycloalkyl with substituents at positions 3 and 4  
 which are independently selected from the group  
 consisting of hydrogen, hydroxyl, O-(C1-C4)-alkyl or  
 15 O-(C1-C4)-alkenyl and carbonyl;

wherein Ar is selected from the group  
 consisting of 1-naphthyl, 2-naphthyl, 2-furyl, 3-  
 furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl,  
 4-pyridyl and phenyl, monocyclic and bicyclic  
 20 heterocyclic ring systems with individual ring sizes  
 being 5 or 6 which may contain in either or both  
 rings a total of 1-4 heteroatoms independently  
 selected from oxygen, nitrogen and sulfur; wherein  
 Ar may contain one to three substituents which are  
 25 independently selected from the group consisting of  
 hydrogen, halo, hydroxyl, hydroxymethyl, nitro, CF<sub>3</sub>,  
 trifluoromethoxy, (C1-C6)-straight or branched alkyl  
 or (C1-C6)-straight or branched alkenyl, O-(C1-C4)-

straight or branched alkyl or 0-(C1-C4)-straight or branched alkenyl, 0-benzyl, 0-phenyl, amino, 1, 2-methylenedioxy, carbonyl and phenyl;

wherein L is either hydrogen or U; M is either oxygen or CH-U, provided that if L is hydrogen, then  
5 M is CH-U, or if M is oxygen then L is U;

wherein U is hydrogen, 0-(C1-C4)-straight or branched alkyl or 0-(C1-C4)-straight or branched alkenyl, (C1-C6)-straight or branched alkyl or (C1-  
10 C6)-straight or branched alkenyl, (C5-C7)-cycloalkyl, (C5-C7)-cycloalkenyl substituted with (C1-C4)-straight or branched alkyl or (C1-C4)-straight or branched alkenyl [(C1-C4)-alkyl or (C1-C4)-alkenyl]-Ar or Ar (Ar as described above);

wherein J is hydrogen or C1 or C2 alkyl or benzyl; K is (C1-C4)-straight or branched alkyl, benzyl or cyclohexylmethyl; or wherein J and K may be taken together to form a 5-7 membered heterocyclic ring which may contain an oxygen (O),  
20 sulfur (S), SO or SO<sub>2</sub> substituted therein;

wherein n is 0-3; and

wherein said pipecolic acid derivative has an affinity for FKBP-type immunophilins, said  
25 administering stimulates growth of damaged peripheral nerves or promotes neuronal regeneration, the FKBP-type immunophilin exhibits rotamase activity, and the pipecolic acid derivative

inhibits said rotamase activity of the immunophilin.

2. The method of claim 1, wherein the neuronal activity is selected from the group consisting of stimulation of damaged neurons, promotion of neuronal regeneration, prevention of neurodegeneration and treatment of neurological disorders.

3. The method of claim 2, wherein the neurological disorder is selected from the group consisting of peripheral neuropathies cause by physical injury or disease state, physical damage to the brain, physical damage to the spinal cord, stroke associated with brain damage, and neurological disorders relating to neurodegeneration.

4. The method of claim 3, wherein the neurological disorder is selected from the group consisting of Alzheimer's Disease and Parkinson's Disease.

5. The method of claim 1, wherein the pipecolic acid derivative compound is immunosuppressive or non-immunosuppressive.

6. A method of treating a neurological activity in an animal, comprising:

administering to an animal an effective amount of a pipecolic acid derivative according to claim 1 having an affinity for FKBP-type immunophilins in combination with an effective amount of a neurotrophic factor selected from the group consisting of neurotrophic growth factor, brain derived growth factor, glial derived growth factor, ciliai neurotrophic factor, and neurotrophin-3, to stimulate growth of damaged peripheral nerves or to promote neuronal regeneration, wherein the FKBP-type immunophilin exhibits rotamase activity and the pipecolic acid derivative inhibits said rotamase activity of the immunophilin.

15

7. The method of claim 6, wherein the neuronal activity is selected from the group consisting of stimulation of damaged neurons, promotion of neuronal regeneration, prevention of neurodegeneration and treatment of neurological disorders.

20

8. The method of claim 7, wherein the neurological disorder is selected from the group consisting of peripheral neuropathies caused by physical injury or disease state, physical damage to the brain, physical damage to the spinal cord, and neurological disorders relating to neurodegeneration.

25

9. The method of claim 6, wherein the neurological disorder is selected from the group consisting of Alzheimer's Disease and Parkinson's Disease.

5 10. The method of claim 6, wherein the pipecolic acid derivative compound is immunosuppressive or non-immunosuppressive.

10 11. A method of stimulating growth of damaged peripheral nerves, comprising;  
administering to damaged peripheral nerves an effective amount of a pipecolic acid derivative compound according to claim 1 having an affinity for FKBP-type immunophilins to  
15 stimulate or promote growth of the damaged peripheral nerves, wherein the FKBP-type immunophilins exhibit rotamase activity and the pipecolic acid derivative inhibits said rotamase activity of the immunophilin.

20 12. The method of claim 11, further comprising administering a neurotrophic factor to stimulate or promote growth of the damaged peripheral nerves selected from the group consisting of neurotrophic  
25 growth factor, brain derived growth factor, glial derived growth factor, ciliary neurotrophic factor, and neurotrophin-3.



13. The method of claim 11, wherein the pipecolic acid derivative is immunosuppressive or non-immunosuppressive.

5 14. A method for promoting neuronal regeneration and growth in animals, comprising:  
administering to an animal an effective amount of a pipecolic acid derivative compound according to claim 1 having an affinity for  
10 FKBP-type immunophilins to promote neuronal regeneration, wherein the FKBP-type immunophilins exhibit rotamase activity and the pipecolic acid derivative inhibits said rotamase activity of the immunophilin.

15 15. The method of claim 14, further comprising administering an effective amount of a neurotrophic factor to promote neuronal regeneration selected from the group consisting of neurotrophic growth  
20 factor, brain derived growth factor, glial derived growth factor, and neurotrophin-3.

16. The method of claim 14, wherein the pipecolic acid derivative compound is immunosuppressive or  
25 non-immunosuppressive.

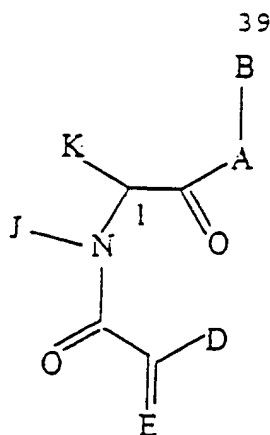
17. A method for preventing neurodegeneration in an animal, comprising:

administering to an animal an effective amount  
of a pipecolic acid derivative according to  
claim 1 having an affinity for FKBP-type  
immunophilins to prevent neurodegeneration,  
5 wherein the FKBP-type immunophilin exhibits  
rotamase activity and the pipecolic acid  
derivative inhibits said rotamase activity of  
the immunophilin.

10 18. The method of claim 17, further comprising  
administering an effective amount of a neurotrophic  
factor to prevent neurodegeneration selected from  
the group consisting of neurotropic growth factor,  
brain derived growth factor, glial derived growth  
15 factor, ciliary neurotrophic factor, and neurotrophin-  
3.

19. The method of claim 17, wherein the pipecolic  
20 acid derivative compound is immunosuppressive or  
non-immunosuppressive.

20. The method of treating a neurological activity  
25 according to claim 1 represented by the formula:



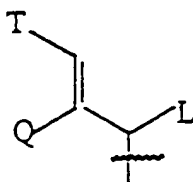
5

and pharmaceutically acceptable salts thereof,

10            wherein A is O, NH, or N-(C1-C4 alkyl);

          wherein B is hydrogen, CHL-Ar, (C1-C6)-straight  
or branched alkyl, (C1-C6)-straight or branched  
alkenyl, (C5-C7)-cycloalkyl, (C5-C7)-cycloalkenyl or  
Ar substituted (C1-C6)-alkyl or alkenyl, or

15



          wherein L and Q are independently hydrogen,  
20            (C1-C6)-straight or branched alkyl or (C1-C6)-  
straight or branched alkenyl;

          wherein T is Ar or substituted cyclohexyl with  
substituents at positions 3 and 4 which are  
independently selected from the group consisting of  
25            hydrogen, hydroxyl, O-(C1-C4)-alkyl or O-(C1-C4)-  
alkenyl and carbonyl;

          wherein Ar is selected from the group  
consisting of 1-naphthyl, 2-naphthyl, 2-furyl, 3-

**SUBSTITUTE SHEET (RULE 26)**

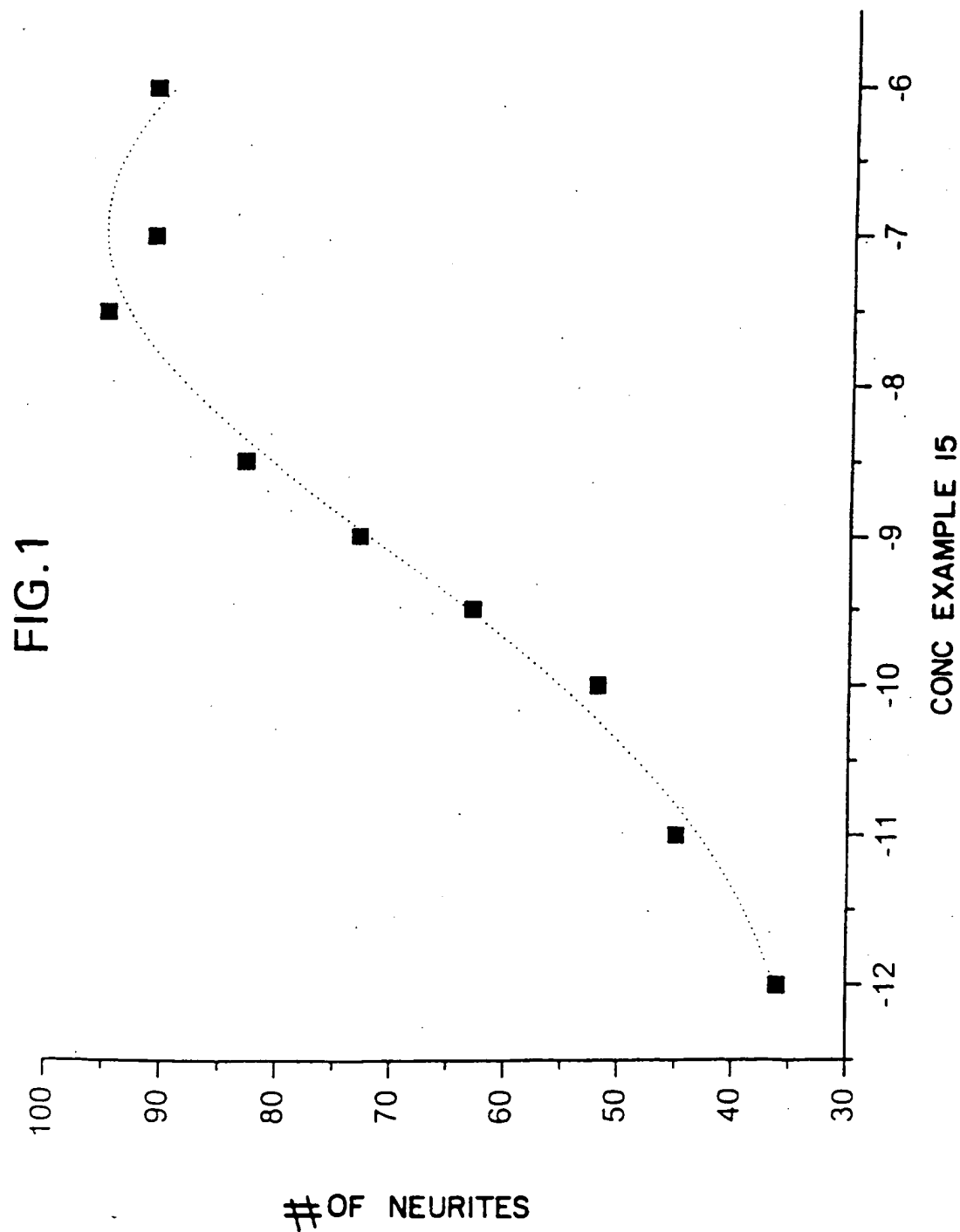
furyl, 2-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl and phenyl having one to three substituents which are independently selected from the group consisting of hydrogen, halo, hydroxyl, nitro, CF<sub>3</sub>, (C1-C6)-  
5 straight or branched alkyl or (C1-C6)-straight or branched alkenyl, O-(C1-C4)-straight or branched alkyl or O-(C1-C4)-straight or branched alkenyl, O-benzyl, O-phenyl, amino and phenyl.

wherein D is either hydrogen or U; E is either  
10 oxygen or CH-U, provided that if D is hydrogen, then E is CH-U, or if E is oxygen then D is U;

wherein U is hydrogen, O-(C1-C4)-straight or branched alkyl or O-(C1-C4)-straight or branched alkenyl, (C1-C6)-straight or branched alkyl or (C1-  
15 C6)-straight or branched alkenyl, (C5-C7)-cycloalkyl, (C5-C7)-cycloalkenyl substituted with (C1-C4)-straight or branched alkyl or (C1-C4)-straight or branched alkenyl, 2-indolyl, 3-indolyl, [(C1-C4)-alkyl or (C1-C4)alkenyl]-Ar or Ar (Ar as  
20 described above);

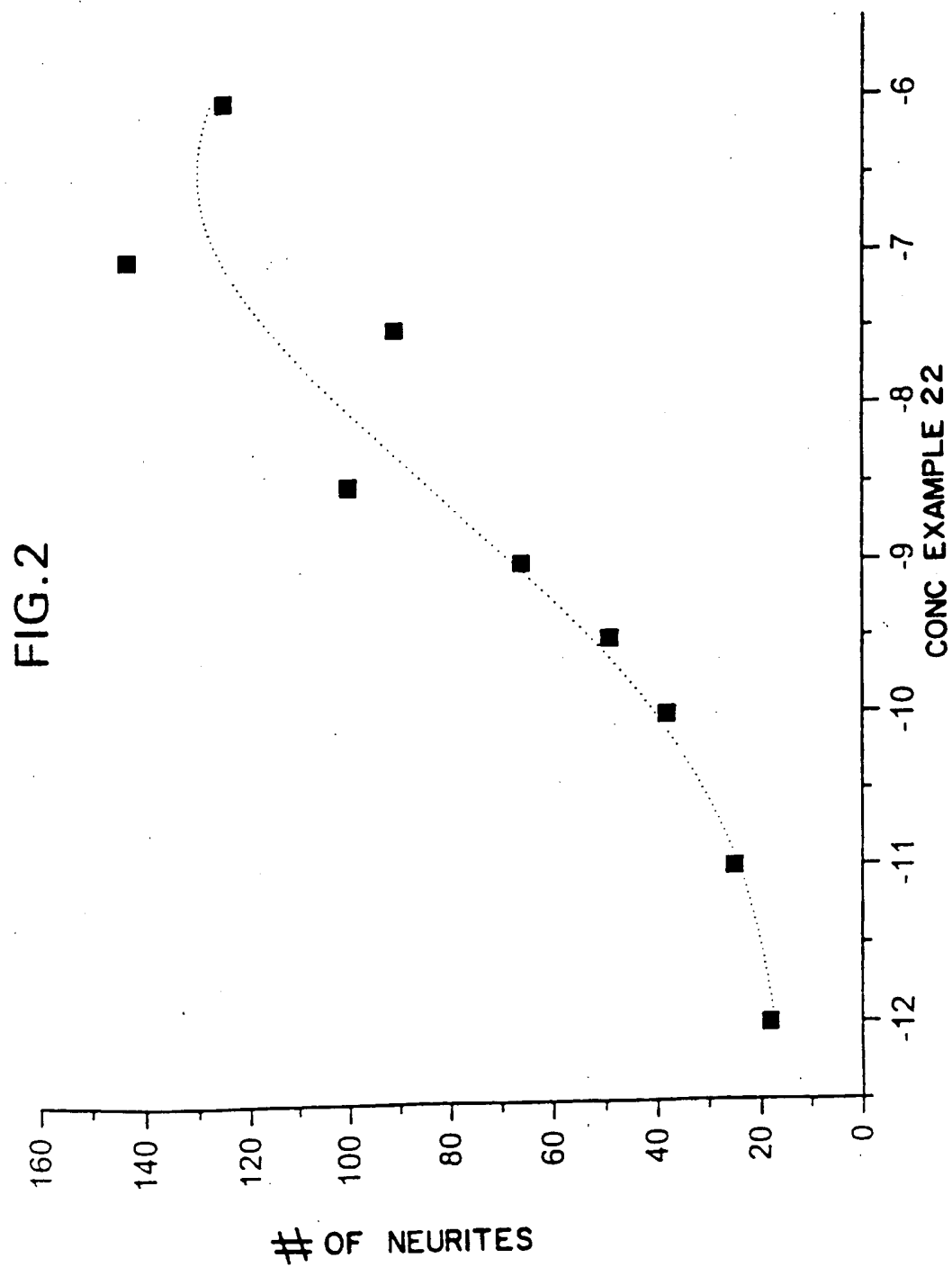
wherein J is hydrogen or C1 or C2 alkyl or benzyl; K is (C1-C4)-straight or branched alkyl, benzyl or cyclohexylethyl; or wherein J and K may be taken together to form a 5-7 membered heterocyclic  
25 ring which may contain an oxygen (O), sulfur (S), SO or SO<sub>2</sub> substituted therein.

1 / 5



SUBSTITUTE SHEET (RULE 26)

2 / 5



SUBSTITUTE SHEET (RULE 26)

3 / 5

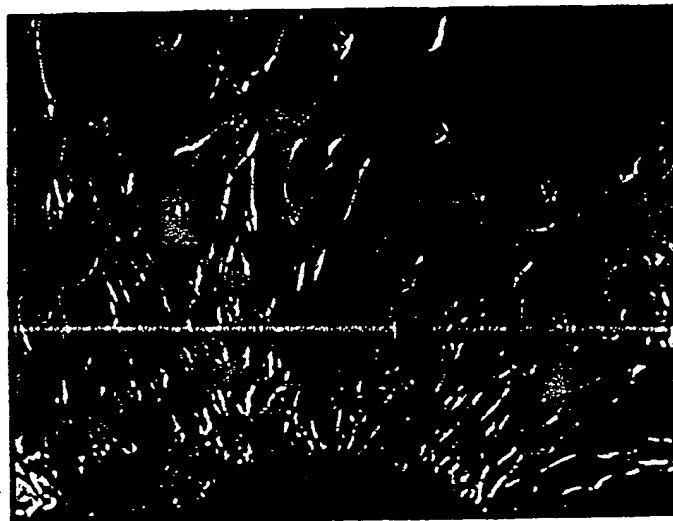


FIG.3C



FIG.3B

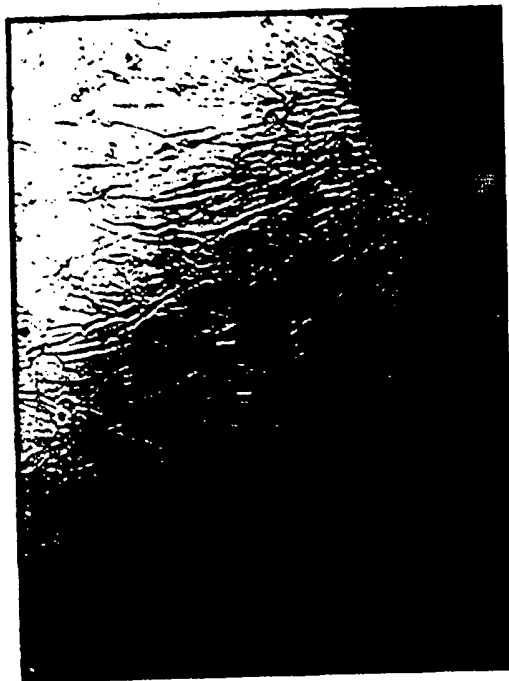


FIG.3A

SUBSTITUTE SHEET (RULE 26)

4 / 5

FIG.4



SUBSTITUTE SHEET (RULE 26)



5 / 5

FIG.5



SUBSTITUTE SHEET (RULE 26)

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US96/13624

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 31/445, 31/40  
US CL : 514/330, 423, 428, 885  
According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/330, 423, 428, 885

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN CAS ONLINE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,330,993 A (ARMISTEAD ET AL.) 19 July 1994, column 4, line 10.	1-20
A	US 4,535,167 A (FREIDINGER) 13 August 1985, column 6, Table 1.	1-20
Y	US 5,192,773 A (ARMISTEAD ET AL.) 09 March 1993, column 3, line 25.	1-20

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*E* earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*G* document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means	
*P* document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search  
26 NOVEMBER 1996

Date of mailing of the international search report  
04 DEC 1996

Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231  
Facsimile No. (703) 305-3230

Authorized officer  
KEITH MACMILLAN  
Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)\*